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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/631,896	PREISSNER ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *4-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/1/03, 11/18/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group I, claims 1-3, in the reply filed on 10/7/2005 is acknowledged. Applicant asserts that a search can be made without undue burden because a literal search for these groups would be largely coextensive. Applicant asserts that a thorough search for the pharmaceutical preparations of claims 1-3 should also involve a search for methods or diagnostic aids that directly utilize the pharmaceutical preparations. Applicant asserts that a thorough search for one type of RNA analog would also involve a search for another type of RNA analog. Applicant asserts that the classification of groups I-XI into the same class and subclass indicates the coextensive nature of these groups.

Contrary to applicant's assertions, a literal search for each of the groups is each separate and distinct. A search for the pharmaceutical preparations of claims 1-3 would not necessarily involve the search of a method or diagnostic aids that add new elements to the search. Additionally, each of the RNA analogs is structurally and functionally unique. Each of the analogs function through different, unrelated mechanisms. A search for the elected RNA analog, peptide nucleic acids, would not involve a search for ribozymes, aptamers, or any other RNA analog that does not meet the structural or functional limitations of a peptide nucleic acid. Additionally, although each of the groups are classified in the same class and subclass, this class and subclass contain many thousands of patents encompassing a multitude of inventions that would each require a separate search and examination. Classification into the same class and subclass does

not mean that any invention within that class and subclass would necessarily return art against another invention.

The requirement for restriction is still deemed proper and is therefore made FINAL.

Claims 4-9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Additionally, the subject matter of claim 1 that is not specifically drawn to peptide-nucleic acids is withdrawn as being drawn to nonelected inventions. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/7/2005.

Instant claim 1 reads "A pharmaceutical preparation which comprises an amount, sufficient for promoting coagulation, of natural or synthetic RNA or of one or more coagulation-promoting fragments of natural or synthetic RNA, RNA analogs, peptide-nucleic acids, ribozymes or RNA aptamers." Applicant has elected peptide nucleic acids. Therefore, the claim is being read as "A pharmaceutical preparation which comprises an amount, sufficient for promoting coagulation, of peptide-nucleic acids."

Priority

It is noted that applicant has claimed foreign priority to two documents, Germany 10236038.3 and Germany 10309368.0. Applicant cannot rely upon the foreign priority papers to overcome the following rejections because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for promotion of coagulation *in vitro* using RNA as a procoagulant cofactor, does not reasonably provide enablement for the treatment of a disease or disorder associated with coagulation via the administration of a pharmaceutical composition *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The invention of the above claims is drawn to pharmaceutical preparations comprising an amount, sufficient for coagulation, of peptide-nucleic acids, further comprising an activator for a plasma coagulation factor, wherein the activator comprises factor VII activating protease or its proenzyme.

The language "pharmaceutical preparation" in claims 1-3 implies a therapeutic or treatment benefit that is not enabled. The *in vivo* promotion of coagulation and resultant treatment effect described in the specification involves prophetic examples only and has not been reduced to practice.

There is no guidance in the specification as filed that teaches how to administer the claimed pharmaceutical composition to cells or tissues *in vivo* and result in

increased coagulation and a therapeutic or treatment effect. Additionally, the instant specification has not taught how a peptide-nucleic acid promotes coagulation. The specification teaches that extracellular RNA represents an important initial cofactor for induction of the coagulation cascade. The specification further teaches that pharmaceutical preparations have been developed in which natural or synthetic RNA or bioactive fragments of the RNA are added to promote hemostasis, however the specification also teaches that RNA-degrading and inhibiting compounds can inactivate the cofactor RNA, resulting in the RNA no longer being available for activation of FSAP or the contact system. The specification teaches that RNA-degrading or masking compounds can thus display important therapeutic effects which prevent initiation of the coagulation system and thus have pronounced anticoagulant effect. Since peptide-nucleic acids are known to target and inhibit RNA with increased specificity, the specification has not taught how one could predictably promote coagulation by administering a pharmaceutical composition comprising a peptide-nucleic acid. The only guidance given in the specification regarding such a mechanism is a statement that "ribonucleases might also display an anticoagulant effect on ribozymes or aptamers, because these substances might bring about, similar to natural RNA, contact phase activation".

The specification does not offer guidance to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by the instantly claimed pharmaceutical preparations, and further does not offer guidance as to how a peptide-nucleic acid would predictably promote, rather than inhibit coagulation.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense and peptide-nucleic acid compounds. Braasch et al. (Biochemistry, Vol. 41, No. 14, 2002, pages 4503-4510) teach that that gene inhibition by antisense oligomers has not proven to be robust or generally reliable technology. Braasch et al. teach that there are a limited number of freely accessible target regions, requiring screening of 20 or more oligomers before identifying one that functions adequately. Braasch stresses that even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different the doses that lead to nonselective toxicity and cell death. Ray et al. (The FASEB Journal, Vol. 14, 2000, pages 1041-1060) teach that peptide nucleic acids hold promise for antisense therapy, but the delivery of PNA, involving passage through the cell membrane, appears to be a general problem (see abstract). Green et al. (Antisense Therapy in Human Disease; Vol. 191, No. 1 2000, pg 103 column 2) teach that "[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more problematic than might be predicted based on preclinical studies in rodents. Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

As outlined above, it is well known that there is a high level of unpredictability in the antisense art, for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely a therapeutic effect of a peptide-nucleic acid and a correlation between peptide-nucleic acids and increase of coagulation.

In view of the unpredictability in the art of antisense-based therapy, as outlined above, the specification as filed does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention without undue experimentation. One of skill in the art would be forced to resort to undue trial and error experimentation.

Given the teachings of the specification as discussed above, one skilled in the art could not predict *a priori* whether introduction of peptide-nucleic acids *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful targeting *in vivo* or enhancement of coagulation. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the peptide-nucleic acid molecule *in vivo*, delivery of the peptide-nucleic acid molecule to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention. Amendment to eliminate "pharmaceutical" from the

preamble and recitation of "in combination with pharmaceutically acceptable diluents" would obviate this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Shimkets et al. (WO 00/58473), as evidenced by Braasch et al. (Biochemistry, Vol. 41, No. 14, 2002, pages 4503-4510).

The invention of the above claim is drawn to a pharmaceutical preparation comprising an amount, sufficient for promoting coagulation, of peptide-nucleic acids.

Shimkets et al. teach ORFX peptide nucleic acids (PNAs) and teach that PNAs have been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength (see page 25, for example). Shimkets et al. teach that the nucleic acid molecules of the invention can be incorporated into pharmaceutical compositions suitable for administration (see page 46). Shimkets et al. teach that the nucleic acids of the invention may be used to enhance coagulation. Additionally, any PNA in a high enough concentration would lead to toxicity, followed by cellular death and coagulation. As evidenced by Braasch et al., "...even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much

different the doses that lead to nonselective toxicity and cell death." (see page 4503). Therefore, any PNA of the prior art formulated in a pharmaceutical composition would qualify as prior art when present in a high enough concentration to induce toxicity, since toxicity is correlated to a promotion of coagulation, as instantly recited. Therefore, the instant invention is anticipated by Shimkets et al.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Moore et al. (US 6,248,724 B1).

The invention of the above claim is drawn to a pharmaceutical preparation comprising an amount, sufficient for promoting coagulation, of peptide-nucleic acids.

Moore et al. teach antisense oligonucleotides and antisense peptide nucleic acid compositions to specifically inhibit ACE gene expression. Moore et al. teach pharmaceutical compositions comprising the peptide nucleic acid. Any PNA in a high enough concentration would lead to toxicity, followed by cellular death and coagulation. As evidenced by Braasch et al., "...even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different the doses that lead to nonselective toxicity and cell death." (see page 4503). Therefore, any PNA of the prior art formulated in a pharmaceutical composition would qualify as prior art when present in a high enough concentration to induce toxicity, since toxicity is correlated to a promotion of coagulation, as instantly recited. Therefore, the instant invention is anticipated by Moore et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimkets et al. (WO 00/58473), in view of Kannemeier et al. (Eur. J. Biochem., 268, 2001, pages 3789-3796).

The invention of the above claims is drawn to pharmaceutical preparations comprising an amount, sufficient for coagulation, of peptide-nucleic acids, further comprising an activator for a plasma coagulation factor, wherein the activator comprises factor VII activating protease or its proenzyme.

Shimkets et al. teach ORFX peptide nucleic acids (PNAs) and teach that PNAs have been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength (see page 25, for example). Shimkets et al. teach that the nucleic acid molecules of the invention can be incorporated into pharmaceutical compositions suitable for administration (see page 46). Shimkets et al. teach that the nucleic acids of the invention may be used to enhance coagulation. Shimkets et al. do not teach specific embodiments wherein peptide nucleic acids have proven to increase coagulation and the teachings of Shimkets et al. regarding peptide nucleic acids are considered to prophetic and as enabled as the instant specification. The PNA or antisense oligonucleotide taught by Shimkets et al. is considered to meet the instant

limitation of an activator for a plasma coagulation factor, since the instant specification discloses that any RNA is a potential activator for a plasma coagulation factor.

Shimkets et al. do not teach specifically teach an activator for a plasma coagulation factor, wherein the activator is factor VII activating protease or its proenzyme.

Kannemeier et al. teach FSAP and FSAP proenzyme. Kannemeier et al. teach that FSAP and its proenzyme play a role in hemostasis and coagulation. Kannemeier et al. teach that when coagulation factor VII is activated by FSAP, coagulation is accelerated.

It would have been obvious to one of ordinary skill in the art to incorporate FSAP or FSAP proenzyme, as taught by Kannemeier et al. into the pharmaceutical composition comprising a PNA taught by Shimkets et al.

One would have been motivated to add FSAP or FSAP proenzyme into the pharmaceutical composition comprising a PNA taught by Shimkets et al., since the pharmaceutical composition of Shimkets et al. was designed to enhance coagulation, for example after trauma or hemophilia. Kannemeier et al. teach that FSAP activates coagulation factor VII, thereby accelerating coagulation, so one would have been motivated to further enhance coagulation by adding FSAP to the pharmaceutical composition as taught by Shimkets et al. Since both the pharmaceutical composition taught by Shimkets et al. and FSAP and FSAP proenzyme taught by Kannemeier et al. enhance coagulation, one would have been motivated to increase the effect by combining the two.

Finally, one would have a reasonable expectation of success given that both the pharmaceutical composition taught by Shimkets et al. and FSAP or FSAP proenzyme, as taught by Kannemeier et al. each are taught to have the benefit of enhancing coagulation. One would expect for such components to benefit a pharmaceutical composition intended for enhancing coagulation and one would expect an increased effect.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Amy H. Bowman
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